REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 332-338, 342, 352 and 367-403 are in the case.

I. THE INTERVIEWS

At the outset, the applicants wish to express their sincere appreciation to the Examiner (Examiner Le) and her supervisor (Examiner Parkin) for the time they have spent in reviewing this case and discussing the issues with the applicants and their counsel over the course of several interviews.

The interviews were conducted on January 10, 2005, May 25, 2005, June 1, 2005, and June 8, 2005. No interview summary record was produced in regard to the interview conducted on January 10, 2005. During this interview, the Examiner advised that the lack of enablement rejection had been overcome by the Amendment dated October 18, 2005. The Examiner further advised that six new references had been developed, the details of which were contained in a paper telefaxed to the undersigned on January 10, 2005. The Examiner requested the Applicants to submit their comments regarding the references, and this was done. The Examiner then contacted the undersigned by telephone to advise that a new non-final action would be issuing raising new prior art rejections.

The second interview was a personal interview conducted on May 25, 2005 with the Examiner and her supervisor, and was attended by Dr. Lorence, Mr. Byrne and the undersigned. The interview summary record dated June 1, 2005, including the Continuation Sheet, reflects the substance of that interview. During this interview, it

was also pointed out that the company to which the subject application is assigned has taken systemic administration of NDV virus for treatment of cancer through phase I clinical trials (of record), and will commence a phase II trial in the near future. Applicant presented proposed amendment to the claims, which included the limitation "more than one dose" in certain claims, and asserted that "subcutaneous" administration of NDV described in Cassel et al was not systemic administration of NDV. In support of this position, Dr. Lorence presented several references, Chen et al., Schirrmacher et al., Morrissey et al., Jia et al., and Crystal et al. Additional references submitted by Applicant were Harrington et al., Yotnda et al., Kirn et al. (of record), and Vile et al.

To properly consider Applicant's presentation, the Examiners requested postponement of the interview until June 1, 2005, when a continuation of the interview (by telephone) was scheduled. Prior to the June 1, 2005 interview, applicant prepared a revised set of claims with certain claims incorporating "consisting essentially of" language as discussed at the May 25, 2005 interview, and presenting additional new claims. That revised set of claims was telefaxed to the Examiner and her supervisor prior to the telephone interview scheduled for June 1, 2005.

Shortly after the June 1, 2005 telephone interview had begun, the Examiners drew attention to Bart et al. At the request of the undersigned, a copy of this reference was forwarded to undersigned by telefax, along with a copy of a further reference to Eaton et al. The interview was again adjourned, and rescheduled for June 8, 2005. The interview summary record for the June 1, 2005 interview, including the Continuation Sheet, reflects the substance of that interview.

Prior to the June 8, 2005 interview, a further revised set of claims was prepared for discussion purposes and telefaxed to the Examiner and her supervisor. A personal interview was conducted on June 8, 2005 with the Examiner and her supervisor, and Mr. Byrne, Dr. Lorence and the undersigned were in attendance. At that interview, agreement was reached as reflected by the Interview Summary Record. The interview summary record for the June 8, 2005 interview, including the Continuation Sheet, reflects the substance of that interview. In particular, agreement was reached:

(1) That the outstanding rejections over Cassel et al. would be withdrawn in view of the amendments presented by the applicant.

(2). That neither Bart et al. nor Eaton et al. disclose tumor regression - Bart et al. relates to inhibition of tumor growth, and Eaton et al. describes immunization.

(3). That Applicant would provide a statement concerning Applicants intended meaning of "consisting essentially of", "purified" and "systemic administration".

(4). That the claims presented for discussion purposes at the interview were viewed by the Examiner and her supervisor as free of the prior art provided that the claims presented at the interview for discussion purposes were amended as discussed, namely draft claims 384-385 would be cancelled without prejudice and the dependencies of remaining claims corrected accordingly, draft claim 397 (new claim 388) would be amended to recite "purified' and "in an amount sufficient to cause tumor regression"; and draft claim 398 (new claim 389) would be amended to recite "purified", "systemic", and "in an amount sufficient to cause tumor regression".

5. That, with regard to the double patenting rejection, since it appears that the instant application is moving towards allowance sooner than the conflicting application, Applicant need not submit a terminal disclaimer for the present application.

The outstanding rejections will now be specifically addressed in light of the agreements reached at the June 8, 2005 interview.

II. THE ANTICIPATION REJECTION

Claims 332-333 (with regard to melanoma), 335, 338-339, 343-344 (with regard to melanoma), and 346, 349-350 stand rejected under 35 U.S.C. 102(b) as allegedly anticipated by Cassel et al. (Cassel et al. A ten-year follow-up on stage II malignant melanoma patients treated postsurgically with Newcastle disease virus oncolysate. Med. Oncol. Tumor Pharmacother. 9 (4): 169-71, 1992). Withdrawal of this rejection is believed in order in light of agreement (1) in the interview Summary Record dated June 8, 2005.

The method as claimed in claim 332 is a method of treating cancer in a mammal having a tumor comprising administering intravenously to the mammal more than one dose of a live purified Newcastle Disease Virus in an amount sufficient to cause tumor regression.

Claim 375 claims a method of treating cancer in a mammal having a tumor comprising administering systemically to the mammal more than one dose of a composition consisting essentially of a live Newcastle Disease Virus in an amount sufficient to cause tumor regression.

Claim 388 claims a method of treating cancer in a mammal having a tumor comprising administering systemically to the mammal a composition comprising a live purified Newcastle Disease Virus in an amount of about 4×10^{10} to 4×10^{12} PFU/kg sufficient to cause tumor regression.

Claim 389 claims a method of treating cancer in a mammal having a tumor comprising administering systemically to the mammal a live purified Newcastle Disease Virus and a chemotherapeutic agent in an amount sufficient to cause tumor regression.

Pursuant to the agreement reached in the June 8, 2005 interview, the term "purified", as used in the independent claims to qualify "Newcastle Disease Virus" (NDV), refers to NDV purified to the extent obtainable using the procedures specified on page 8, lines 18-21 and in Example 1 of the specification.

The term "systemically", as used to qualify the term "administering" in claims 375, 388 and 389, refers to administration that is not local or regional (see page 13 lines 8-10 of the specification). Examples of systemic administration include, but are not limited, to intraperitoneal, intravenous and exclude subcutaneous and intratumoral administrations.

The phrase "consisting essentially of" has been defined by the PTO Board of Appeals in Ex parte Davis 80 USPQ 448 (1949) as " rendering the claim open only for the inclusion of unspecified ingredients which do not materially affect the basic and novel characteristics of the composition." This phrase as used in the subject claims "composition consisting essentially of Newcastle Disease Virus" distinguishes the NDV composition of the claims from the compositions of the prior art such as Cassel et al. which relates to administration of a viral oncolysate cell mixture, or Bart et al. which

relates to administration of virus and allantoic fluid, since in these prior art instances, the NDV compositions include ingredients which "materially affect the basic and novel characteristics of the composition."

Cassel does not teach Systemic Administration of the NDV Virus

The Examiner asserts that "The method of administration used by Cassel et al. is subcutaneous administration, which is a systemic mode of administration." This position is respectfully traversed.

The disclosure by Cassel of subcutaneous administration of a viral oncolysate (a) is not intravenous administration to a mammal having a tumor of live purified Newcastle Disease Virus (claim 332), (b) is not systemic administration to a mammal having a tumor of a composition consisting essentially of a live Newcastle Disease Virus (claim 375 or 388) and (c) is not systemic administration to a mammal having a tumor of a live purified Newcastle Disease Virus and a chemotherapeutic agent (claim 389). Cassel's methodology involves taking tumor cells, infecting the tumor cells *ex vivo* with NDV and then administering this mixture of viral infected tumor cells (termed "viral oncolysate") back to the patient via subcutaneous injection at a time that the patient is free of any detectable tumor. Cassel does not make any mention of systemic administration. This subcutaneous injection is clearly not the same as *systemic or intravenous administratio*n of live purified NDV virus, as presently claimed.

Subcutaneous injection of a virus is not a "systemic" or "intravenous" administration because a virus does not freely diffuse from the subcutaneous space into the circulation (see Jia and Zhou, Curr. Gene Ther., 5:133-142 (2005) (copy attached) which indicates (see Abstract) that: "A major difference between virus-mediated gene

therapy and other therapies is the poor physical diffusibility of viral vectors.") A specific example using adenovirus is described by Morrissey et al. (2002; Toxicology Sciences 65:266-275) (copy attached). In that paper, the authors state:

> "Testing by the sc [subcutaneous] route in rats was done to determine the potential for local irritation at the injection site. Intravenous (iv) dosing was done to stimulate a worst-case scenario in which the dose was systemically administered." [page 266, 2nd from last paragraph; last two sentences].

The Morrissey paper clearly draws a distinction between subcutaneous injection, which Morrissey does not consider to be a form of systemic administration of a virus, and intravenous injection, which Morrissey does consider to be a form of systemic administration of a virus. Injecting a dose of 11×10^{11} adenovirus particles/kg subcutaneously (sc) in rats was well tolerated, only causing some local skin thickening, but "body weight, food consumption, hematology and serum chemistries were not affected by sc dosing". In contrast, the same dose given intravenously caused lethality to some of the rats. Surviving animals showed body weight loss and food consumption decreases along with changes in hematology and serum chemistries with iv dosing. Based on the above observations, one of ordinary skill would not consider the subcutaneous modes of administration of a virus to be systemic.

Further evidence that subcutaneous injection of virus is not a systemic administration is provided in papers by Crystal et al. (2002) and Chen et al. (2002). Crystal et al (beginning with the last sentence on page 93) indicates that "all of the routes used in the present study [including skin injections] were local, whereas most experimental animal studies demonstrating major adverse events in association with adenovirus vectors use systemic (intravascular) administration of the vector." Chen et

al. (Introduction, 2nd paragraph, 3rd and 4th sentences) stated that: "We have been interested in systemic administration of adenovirus for the treatment of metastatic prostate cancer. Such treatment requires intravascular injection of adenovirus to achieve virion distribution to multiple distant tumor sites."

Cassel does not Teach a Method of Treating Cancer in a *Mammal having a Tumor*

The Examiner notes that "Cassel et al. notes that the administration of the viral oncosylate enhances the recurrence-free interval of the tumor in patients that received the viral oncosylate treatment. Thus, the amount of viral oncosylate administered by Cassel et al. is an amount effective to cause tumor regression."

Cassel does not claim or indicate that his treatment causes *tumor regression*. Cassel indicates that administration of "viral oncolysate" via subcutaneous injection is with the aim of *preventing tumor recurrence*. It follows that if the aim is to prevent tumor recurrence then, by definition, the patients do not have any tumors. Cassel treats cancer patients who have had their tumor masses removed surgically. Such patients have a risk of tumor recurrence due to some tumor *cells* remaining in the patient after surgery. Cassel aims to stimulate the immune system to remove such tumor cells. Schirmacher (Schirrmacher, Int J Oncol (1999)15:217-227) (copy attached) suggests that stimulation of the immune system by NDV infected tumor cells is ineffective in treating established tumors since he surgically removes tumors prior to administration of NDV. This is to be contrasted with the presently claimed invention which requires a tumor at the time of treatment.

Based on the above, it is clear that the anticipation rejection should be withdrawn. Such action is respectfully requested.

III. THE OBVIOUSNESS REJECTIONS

Claims 333 (with the exception of melanoma), 334, 366, 344 (with the exception of melanoma), 345, 347, 356, 357, 359-360 and 365-366 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Cassel (1992). Reconsideration is requested.

The Examiner notes that 'the claims limit the tumor to colon adenocarcinoma, neuroblastoma, cervical cancer; and selected from the group consisting of lung carcinoma, breast carcinoma, prostate carcinoma, endometrial carcinoma, ovarian carcinoma, bladder carcinoma, Wilm's tumor, fibrosarcoma, osteosarcoma, melanoma, synovial sarcoma, and glioblastomas." The Examiner further notes that while Cassel does not teach administration of the viral oncolysate to a patient group having various tumors, it is well established that viral oncolysates can be highly effective immunizing agents against challenge by the autogenous tumors. From this, the Examiner concludes that it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to administer viral oncolysate to different patient groups and that one of ordinary skill would have had a reasonable expectation of success for doing so because viral oncolysates can be highly effective immunizing agents against challenge by the autogenous tumors, as further exemplified by Cassel who successfully used viral oncolysate, wherein the virus is NDV, to treat patients having a tumor.

Again, Cassel infects tumor cells *ex vivo* with NDV and then administers this viral oncolysate back to the patient via subcutaneous injection. As noted in detail above with respect to the anticipation rejection, Cassel does not disclose *systemic administration* of live NDV virus, as claimed. Thus, Cassel in no way suggests systemic administration of live NDV in an amount which causes regression of lung carcinoma, breast carcinoma, prostate carcinoma, colon adenocarcinoma, cervical carcinoma, endometrial carcinoma, ovarian carcinoma, bladder carcinoma, Wilm's tumor, fibrosarcoma, osteosarcoma, melanoma, synovial sarcoma, neuroblastoma or glioblastoma in accordance with the methods of this invention.

The Examiner notes at the top of page 5 that [Cassel] "successfully used viral oncolysate, wherein the virus is NDV, to treat patients having a tumor." Applicants respectfully disagree. As note above, Cassel indicates that administration of "viral oncolysate" via subcutaneous injection is with the aim of *preventing tumor recurrence.* Thus, the patients in Cassel do not have any tumors.

The Art Teaches away from Systemic Administration of NDV

Schirrmacher (Int. J. Oncol. 2001, 18:945-52) (see attached) indicates that: "We demonstrate antitumor activity of various NDV strains when applied locally but not after systemic (i.v. or i.p.) application." (last sentence of introduction) (emphasis added). The paper goes on to state that: "The difference between local effectivity and systemic ineffectiveness of NDV in this test system is most likely due to ineffective tumor targeting of NDV upon systemic application" (last sentence on page 590). Schirrmacher clearly makes a distinction between systemic application of NDV and the use of NDV-infected tumor vaccines: "Since direct targeting of tumor metastases by systemic NDV

application appears difficult, targeting of metastases via activated antitumor immune T cells remains another option. Activation of such antitumor immune T cells can be tried either by direct immunization with tumor vaccines as we do (6,7,9-11,30) or by *ex vivo* stimulation in which case immunotherapy would be tried by adoptive transfer of such activated T cells."

The references (6,7,9-11,30) cited by Schirrmacher as being distinct from systemic application of NDV are references involving injections into the skin of NDV-infected tumor cells analogous to the method of Cassel using subcutaneous injections of NDV infected tumor cells. Thus, Schirrmacher, even 8 years after the present invention, and taking into account Cassel's work, leads away from the presently claimed invention of systemic administration of NDV.

Claims 340-341, 353-356 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Cassel et al. in view of Cohen et al. (U.S. Patent No. 5739107). Reconsideration is requested.

The Examiner alleges that Cohen teaches other means of systemic administration, including subcutaneous, intravenous and intraperitoneal methods. The Examiner refers to column 5, lines 55-57 of Cohen which states that the "...morphogen or morphogen-stimulating agent is provided systemically, e.g., by parenteral administration." The Examiner further cites column 21, lines 53-63 which states that "Where the morphogen is to be provided parenterally, such as by intravenous, subcutaneous, intramuscular, intraorbital....."

Cassel does not suggest the presently claimed invention, and the deficiencies of Cassel, as noted above, are not cured by Cohen. Parenteral administration does not

always result in a systemic administration. Cohen is concerned with morphogenic proteins *and not with viruses*. Such proteins may contain in the region of 100 amino acids, in distinct contrast to viruses which contain thousands of proteins and other complex molecules, and are, accordingly, much larger.

Claims 337, 348 and 361-362 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Cassel et al. in view of Hanson et al. (Hanson et al. Identification of vaccine strains of Newcastle disease virus. Science, July 1955, Vol. 122, p. 156-1 57.) Reconsideration is requested.

The Examiner notes that Hanson teaches the MK 107 variant of NDV. Cassel does not suggest the presently claimed invention, and the deficiencies of Cassel, as noted above, are not cured by Hanson.

Claims 342, 351-353 and 363-364 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Cassel et al. in view of Yoshiomi et al. (JP 58-116422). Reconsideration is requested.

The Examiner notes that Yoshiomi teaches that the dose to administer depends on various factors, such as the symptom, dispensing route, and body weight. Cassel does not suggest the presently claimed invention, and the deficiencies of Cassel, as noted above, are not cured by Yoshiomi.

IV. OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

Pursuant to the agreement reached at the interview, it is believed that this rejection should be withdrawn. Such action is respectfully requested.

V. BART ET AL AND EATON ET AL

Neither Bart et al. nor Eaton et al. disclose or suggest the invention as claimed. Both references disclose the administration of NDV in allantoic fluid, which does not meet the requirement of "purified" in claims 332, 388 and 389, and is excluded by the "consisting essentially of language of claim 375. The invention as now claimed is therefore free of Bart et al and Eaton et al.

VI. NEW CLAIMS

Support for the claims as amended and the new claims presented herewith is set forth below with reference to the amended and new claim numbers. No new matter is entered.

332 - Intravenous supported by page 13, line 6 and page 15 line 25; more than one dose supported by page 13 lines 32-33; also by page 27 lines 8-9 and line 19; purified NDV supported by page 23 (line 33) and page 24 (line 27);

342 - Intravenous supported by page 13, line 6 and page 15 line 25;

352 - Intravenous supported by page 13, line 6 and page 15 line 25; 10^8 PFU supported by page 27 line 19;

367 - Chemotherapeutic agent supported by page 14 lines 17-18 and page 34 line 9;

368 - Supported by page 14 lines 19-22;

369 - Supported by page 14 line 22;

370 - Immunosuppressive agent supported by page 15 line 11 and page 34 line 10;

371 - Supported by page 15 line 16;

372 - Supported by page 14 line 15;

373 - Supported by page 14 line 27;

374 - Supported by page 14 line 36;

375 - "Consisting essentially of" discussed during interview dated May 25, 2005; composition supported by page 1 line 14 and page 5 line 14;

376 - Colon adenocarcinoma supported by page 11 lines 15-16; page 29 lines 1-2; and page 31 lines 13-14;

377 - Melanoma supported by page 11 line 18; page 29 lines 5-6; and page 31 lines 28-29;

378 - Neuroblastoma supported by page 6 lines 17 and 28, page 11 line 19; page 25 line 16, and page 28 line 35;

379 - Cervical carcinoma supported by page 11 line 16; page 28 line 29; and page 30 line 36;

380 - MK107 supported by page 6 line 31, page 27 line 32;

381 – intravenous - see above;

382 - 10^8 PFU supported by page 27 line 19;

383 - See support for claim 367;

384 - Supported by page 23 lines 22-34;

385 - Supported by page 23 line 23;

386 - Supported by pages 8 to 10 beginning at page 8 line 24;

387 - See support for claim 379;

388 - Supported by page 13 lines 21-22;

389 - See support for claim 367;

390 - See support for claim 368;.

391 - See support for claim 369.

392 - See support for claim 375;

393 - Supported by page 12 line 30 and page 15 line 22;

394 - Human tumor supported by page 26 line 28 and page 27 line 29;

395 - Supported by page 26 lines 31-32;

396 - Supported by page 11 line 23;

397 - Supported by page 25 lines 17 and 32 and page 27 line 14;

398 - Supported by page 6 lines 31-32;

399 - Radiation supported by page 13 line 31;

400 - See support for claim 384;

401 - See support for claim 385;

402 - See support for claim 386;

403 - Supported by page 25 lines 17 and 32 and page 27 line 14.

Favorable action is awaited.

Respectfully submitted,

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